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Altered Structural Network in Newly Onset Childhood Absence Epilepsy

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Background and Purpose Recent quantitative neuroimaging studies of childhood absence epilepsy (CAE) have identified various structural abnormalities that might be involved in the onset of absence seizure and associated cognitive and behavioral functions. However, the neuroanatomical alterations specific to CAE remain unclear, and so this study investigated the regional alterations of brain structures associated with newly diagnosed CAE.

Methods Surface and volumetric magnetic resonance imaging data of patients with newly diagnosed CAE (n=18) and age-matched healthy controls (n=18) were analyzed using FreeSurfer software. A group comparison using analysis of covariance was performed with significance criteria of $p<0.05$ and $p<0.01$ in global and regional analyses, respectively.

Results Compared with control subjects, the patients with CAE had smaller total and regional volumes of cortical gray-matter (GM) in the right rostral middle frontal, right lateral orbitofrontal, and left rostral middle frontal regions, as well as in the right precentral, right superior, middle, left middle, and inferior temporal gyri. The cortex in the right posterior cingulate gyrus and left medial occipital region was significantly thicker in patients with CAE than in controls.

Conclusions Patients with CAE showed a reduced bilateral frontotemporal cortical GM volume and an increased posterior medial cortical thickness, which are associated with the default mode network. These structural changes can be suggested as the neural basis of the absence seizures and neuropsychiatric comorbidities in CAE.

Key Words absence epilepsy, magnetic resonance imaging, cerebral cortex, gray matter.

INTRODUCTION

Childhood absence epilepsy (CAE) is a common generalized epilepsy syndrome with a presumed genetic cause that is characterized by frequent daily absence seizures, with electroencephalography (EEG) showing bilateral, synchronous, symmetric spike-and-wave discharges at approximately 3 Hz.[1,2] The onset of seizures occurs between the ages of 4 and 8 years, with spontaneous remission around adolescence, and this age-dependent onset and remission means that CAE is regarded as a developmental disorder.[3] Although CAE usually has a favorable prognosis, psychiatric problems such as attention deficit/hyperactivity disorder (ADHD) as well as behavioral problems may occur and persist even in the absence of ongoing seizures.[4]

Recent studies using advanced magnetic resonance imaging (MRI) techniques have revealed that patients with CAE have focal structural abnormalities that are not detected using routine MRI.[5-10] Previous quantitative neuroimaging studies of brain subcortical structures have shown altered volumes of the thalamus or amygdala in patients with CAE.[5,6,8-10] Subsequent studies that applied advanced imaging and analytical techniques to the regional

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gray-matter (GM) and white-matter (WM) volumes and cortical thickness have revealed focal alterations of the volume and cortical thickness mainly in frontotemporal and parietal regions.[7,11,12] Although the results have not been consistent across studies, they support the cortical focus theory stating that absence seizures are initiated by a cortical focus with the secondary involvement of the thalamocortical network.[13] In particular, the frontal and parietal cortices are the main structures involved in absence seizures typified by the generation of diffuse slow-wave complexes.[13-16] Additionally, recent advanced studies using functional MRI (fMRI) and magnetoencephalography have demonstrated diverse functional alterations in the frontoparietal regions involved in the default mode network (DMN) or the frontoparietal attention network, suggesting that CAE is a network disorder.[15-18]

Previous imaging studies involving patients with CAE had several limitations, including involving mixed samples of subjects with idiopathic generalized epilepsy, diverse age groups, and the long-term effects of uncontrolled seizures and chronic use of antiepileptic drugs on brain maturation. In addition, the reported profiles of abnormal structures were inconsistent in studies involving children with CAE.[7,11,12] Therefore, the present study investigated structural alterations in the cortical and subcortical regions in children with newly diagnosed CAE using automated measures of brain MRI in comparison with age- and sex-matched control subjects.

METHODS

Subjects

The research participants comprised 18 children with newly diagnosed CAE [12 females; age at diagnosis, 8.2±1.6 years (mean±SD); age range, 5.4−10.6 years] and 18 age- and sex-matched healthy controls (12 females; age, 8.3±1.6 years; age range, 5.5−10.6 years) at the Children's Hospital, Asan Medical Center, Ulsan University College of Medicine, Korea. The initial selection criteria for each CAE subject included a diagnosis of CAE according to the International League Against Epilepsy classification (Commission, 1989). A diagnosis of CAE was determined by three board-licensed pediatric neurologists who reviewed all available medical records, including seizure semiology and EEG findings. All patients with CAE had EEG evidence of 3-Hz spike-and-wave complexes with a period of >4 s in addition to absence seizures induced by hyperventilation. Other inclusion criteria were 1) no type of epilepsy other than CAE, 2) no other neurological disease, 3) intelligence quotient of 85 or higher, 4) normal findings in standard clinical brain MRI, and 5) not taking antiepileptic drugs at the time of the MRI investigation. This study was reviewed and approved by the Institutional Review Board of Asan Medical Center (approval number 2014-0405). Since all of the subjects were too young to provide consent, all informed consents were given by their parents.

MRI protocol

All subjects underwent MRI scanning (3.0-T Achieva, Philips Healthcare, Eindhoven, the Netherlands) to obtain high-resolution, three-dimensional, whole-brain T1-weighted images, which included scanning in the sagittal plane with an in-plane resolution of 1.0 mm×1.0 mm, slice thickness of 1 mm, echo time of 4.6 ms, repetition time of 9.8 ms, flip angle of 8.0°, and field of view of 224 mm^2. The obtained MRI scans were evaluated by pediatric neuroradiologists who were blind to both the disease status of the subjects and the study hypothesis.

Image analysis

We used FreeSurfer software (version 5.3.0, https://surfer.nmr.mgh.harvard.edu) to perform fully automated surface-based analyses comparing the total brain, GM, and WM volumes (global and regional) and the regional cortical thicknesses between the patients with CAE and healthy controls. The image analysis procedure was similar to those described previously.[19-22] The skull, scalp, extracranial fluid, and meninges were removed from the normalized intensity image generated after correcting for intensity variations. The preliminary segmentation of the brain was then generated using a connected-components algorithm, and any interior holes in the components representing WM were filled. A constructed polygonal surface model was applied to obtain a representation of the GM/WM boundary and the pial surface after a refinement procedure.

The above-described automatic cortical reconstruction and parcellation technique was used to subdivide each hemisphere into 34 gyral labeled areas.[23,24] To improve the accuracy of the imaging analysis, key intermediate processing outputs of FreeSurfer were inspected visually, with brain masks and inaccurate definitions of WM corrected manually where necessary. The cortical thickness was quantified as the closest distance from the GM/WM boundary to the GM/cerebrospinal fluid boundary at each vertex. Global and regional cortical and subcortical GM and WM volumes were calculated using FreeSurfer's automated procedure for making volumetric measurements.

Statistical analysis

The Kruskal-Wallis test and the Mann-Whitney U test for continuous variables (SPSS, version 23.0, IBM Corp., Armonk, NY, USA) were used to assess group differences in the demographic and clinical variables. Statistical maps of the findings

of the image analyses were generated using FreeSurfer's Query, Design, Estimate, Contrast (QDEC) interface. The QDEC interface is a single-binary application built into the FreeSurfer distribution that is used to compare morphological data produced by the FreeSurfer processing stream between groups. For each hemisphere, the general linear model was computed on a vertex-by-vertex based for analyzing the cortical thickness and GM and WM volumes while accounting for the effects of sex and age. Multiple comparisons were corrected using a Monte Carlo simulation method, which is a clusterwise correction method; the initial cluster-forming criterion was set at $p<0.01$. These results corrected for multiple comparisons were considered to be significant when $p<0.05$ for global and $p<0.01$ for regional analyses.

RESULTS

Subject characteristics

The age at seizure onset in the 18 patients with CAE was 7.3±1.5 years (range, 5.3–10.2 years), and their duration of illness was 10.0±3.6 months (range, 0–49 years). Fourteen CAE subjects were right-handed, two were left-handed, and two had unknown handedness. Fifteen control subjects were right-handed, two were left-handed, and one had unknown handedness. There were no significant differences in the body mass index or total brain volume between the CAE subjects and healthy controls.

GM and WM volumes of patients with CAE and controls

Both groups showed age-related increases in total brain and WM volumes, and age-related reductions in total, cortical, and subcortical GM volumes (Fig. 1). The total cortical GM volume was significantly smaller in the patients with CAE than in the control subjects ($p=0.042$) (Fig. 1D). The mean volumes of the total brain, total GM, total WM, and subcortical GM did not differ significantly between the two groups (Fig. 1A–C and E).

The regional volume analysis revealed that the volumes of cortical GM in the right rostral middle frontal, lateral orbitofrontal, precentral, superior and middle temporal, left rostral middle frontal, supramarginal, and middle and inferior temporal gyri were significantly smaller in the patients with CAE than in the controls ($p<0.01$) (Fig. 2, Supplementary Table 1 in the online-only Data Supplement). There were no significant intergroup differences in the regional WM volumes (Supplementary Table 1 in the online-only Data Supplement) or the regional GM volumes of subcortical and limbic structures (Supplementary Table 2 in the online-only Data Supplement).

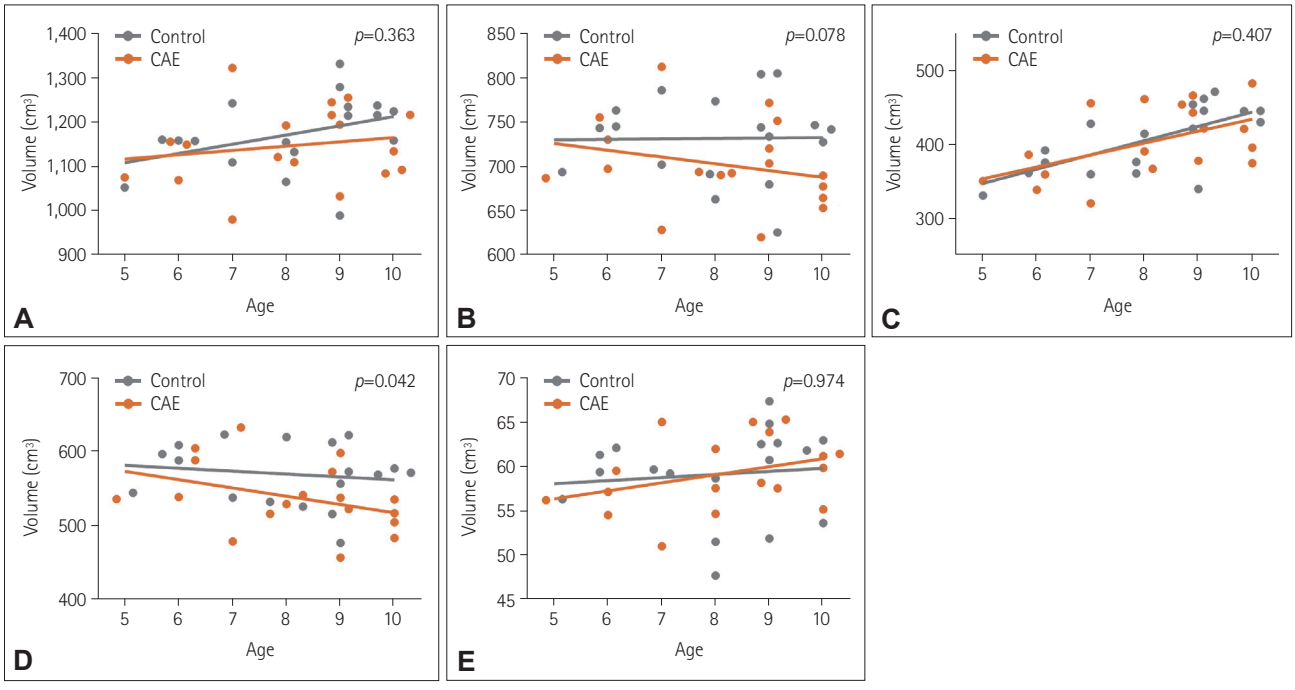

Fig. 1. Comparison of the volumes of brain between patients with CAE and controls. Scatter plots and trend lines of the mean volumes of the (A) total brain, (B) total GM, (C) total WM, (D) cortical GM, and (E) subcortical GM according to age in magnetic resonance imaging evaluations of patients with CAE and control subjects. Both groups show age-related increases in total brain and WM volumes, and age-related reductions in total, cortical, and subcortical GM volumes. (D) The patients with CAE showed a significantly smaller total cortical GM volume compared with control subjects ($p=0.042$). CAE: childhood absence epilepsy, GM: gray-matter, WM: white-matter.

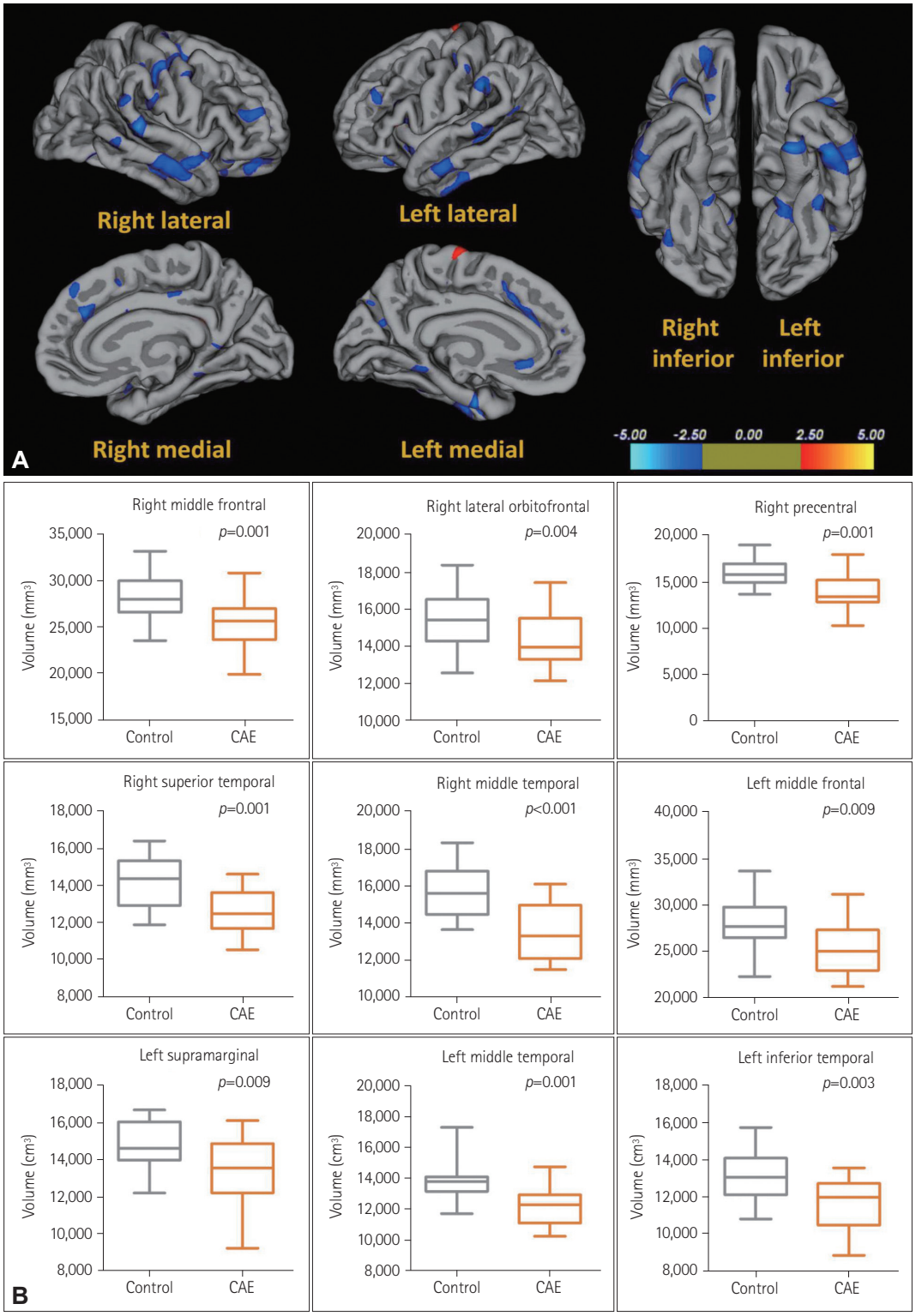

Fig. 2. Illustration of regional differences in cortical GM volumes between patients with CAE and healthy control subjects ($p<0.01$). A: The regions with decreased cortical GM volumes relative to those in the controls in the patients with CAE are shown in blue (color coding reflects t values). B: The cortical GM volumes in the right rostral middle frontal; lateral orbitofrontal; precentral, superior, and middle temporal; and left rostral middle frontal, supramarginal, middle, and inferior temporal gyri were smaller in the patients with CAE than in the controls. Comparisons of cortical volumes (in cubic millimeters) are presented as box plots. Each box plot shows the median (50th percentile; dark bar), values to the 1.5 interquartile range (whiskers) and 25th percentile to 75th percentile range (box). CAE: childhood absence epilepsy, GM: gray-matter.

Cortical thicknesses in patients with CAE and controls

The mean cortical thicknesses of both hemispheres did not differ significantly between the patients with CAE and the controls (Fig. 3). Regional analysis revealed that the cortical thicknesses in the right posterior cingulated gyrus (p=0.004) and the left medial occipital region including the cuneus, pericalcarine, and lingual gyri (p=0.008) were significantly greater in the patients with CAE than in the controls (Fig. 4).

DISCUSSION

This study investigated structural alterations of the brain in patients with CAE and found that the volumes of total cortical GM and regional GM in the bilateral frontotemporal regions were significantly smaller in patients with CAE than in age- and sex-matched control subjects. The patients with CAE also had significantly thicker cortices in the right posterior cingulate gyrus and the left medial occipital region compared with the control subjects. These cortical alterations in different brain regions might be associated with the development of absence seizures with 3-Hz generalized spike-and-wave discharges in this specific age. Discordance between the results of the cortical thickness analysis and the volumetric analysis can be explained by differences between one- and three-dimensional measures, where the latter is also associated with the network topology.[25]

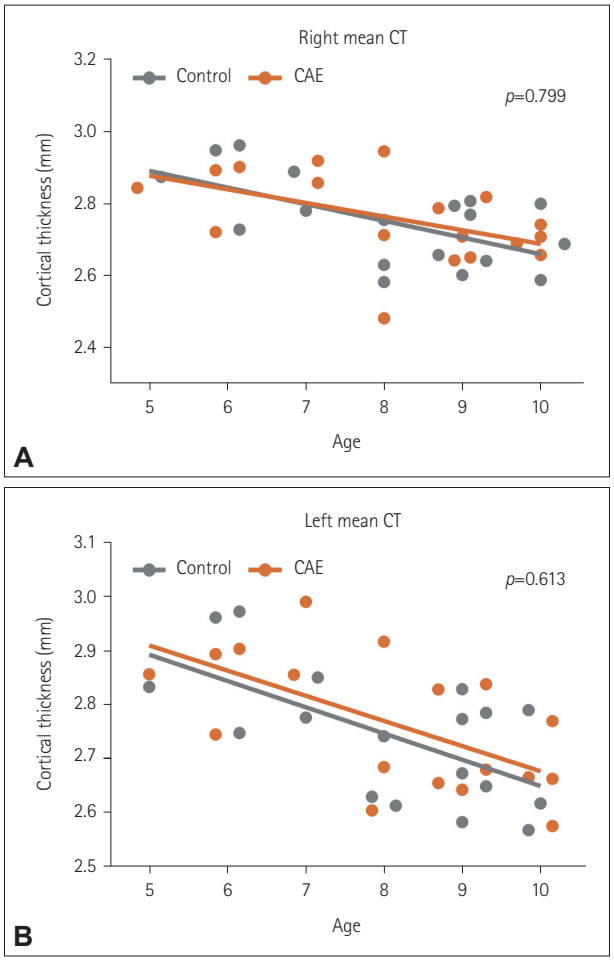

Fig. 3. Scatter plots and trend lines of the mean cortical thickness according to age in magnetic resonance imaging evaluations of patients with CAE and control subjects. Both groups show age-related cortical thinning. However, there was no significant difference between the patients with CAE and the controls in the comparison of the mean cortical thickness of (A) the right and (B) left hemisphere. CAE: childhood absence epilepsy.

The cortical alterations in the posterior cingulated cortex, rostral middle frontal and lateral temporal cortex, and orbitofrontal cortex observed in our study were similar to previously described findings of diverse structural and functional abnormalities in humans and animals exhibiting absence seizures.[7,10-12,26,27] The posterior cingulate gyrus is known to be a central node in the DMN and frontoparietal control networks,[28] and abnormal cortical thickening could be correlated with the clinical symptoms of the CAE. A previous study using fMRI and EEG also suggested that the parietal cortex—rather than the frontal cortex—plays a direct role in the initiation of epileptiform activity in absence seizures.[15] In addition, the lateral temporal cortex is known to participate in the dorsal medial system of the DMN and form a part of the functional network with frontal and parietal regions implicated in spatial attention.[29,30] The rostral middle frontal cortex is also one of the critical nodes of the ventral attention network.[31] Considering the roles of the DMN and frontoparietal control network in attention, goal-oriented cognition, and adaptive control processes,[32] cortical alterations in the middle frontal and lateral temporal regions could be associated with two core features of absence seizures: disruption of attention and awareness. The altered orbitofrontal cortex revealed in this study was also regarded to be important in the generation of absence seizures since it regulates alertness and arousal via its control of the thalamic regulatory mechanisms.[16,33,34]

Based on several longitudinal pediatric neuroimaging studies using recent advanced MRI technology, it has been postulated that age-related maturational changes in the brain are regionally specific, following a posterior-to-frontal progression of development.[35-37] Considering the normal trajectory of cortical development and the age of the patients in the present study, the smaller regional GM volumes in the bilateral frontotemporal regions and the thickened posterior medial cortices in patients with CAE suggest an altered trajectory of cortical development. Although it remains unclear whether this finding is a result of the delayed developmental process

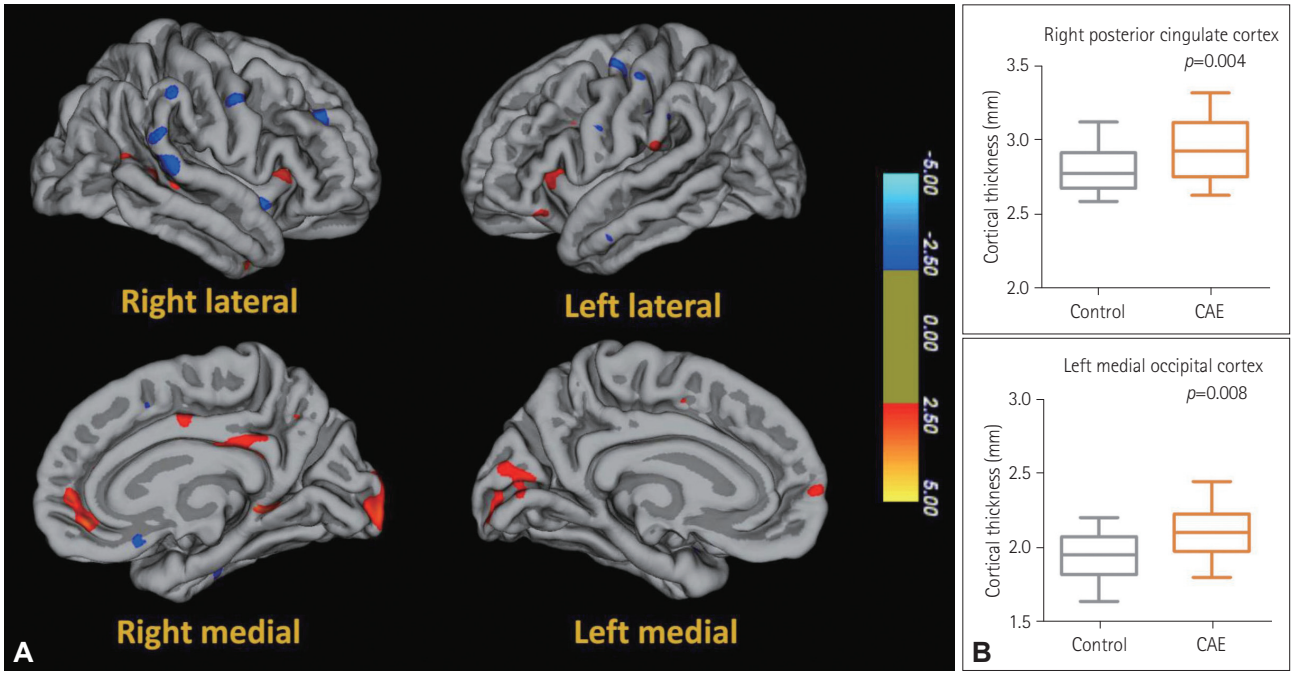

Fig. 4. Regional differences in cortical thickness between patients with CAE and healthy control subjects ($p<0.01$). A: Regions with thicker cortices are shown in red to yellow (color coding reflects *t* values). B: The right posterior cingulated and left medial occipital gyri are significantly thicker in patients with CAE than in the controls. Comparisons of cortical thicknesses (in millimeters) are presented as box plots. Each box plot shows the median (50th percentile; dark bar), values to the 1.5 interquartile range (whiskers) and 25th percentile to 75th percentile range (box). CAE: childhood absence epilepsy.

or an occult cortical malformation, our findings suggest that this altered cortical development can contribute to the onset and turning off of absence seizures at a specific age window during development. Several recent analyses of the brain have suggested that CAE is a disorder of the brain network that forms part of the default state system or attention system.[16,38-41] These analyses have revealed that abnormal functional or structural networks—rather than certain isolated brain regions—are crucial for spike-and-wave discharge generation and propagation in CAE.

This study has also revealed bilateral frontotemporal structural abnormalities with volume reduction and the thicker cortex in the left medial occipital region, which may have important functional implications. From the functional perspective, the involvement of the frontal and temporal lobes in cognition, language, and behaviors/emotions suggests that these alterations contribute to the higher incidence of learning and behavioral difficulties, language delay, attention deficits, and hyperactive-impulsive symptoms in children with CAE.[4,42] The medical occipital cortex including the cuneus, pericalcarine, and lingual gyri is known to play an important role in the visual processing and word processing networks, which are modulated by attention, memory, and emotion.[43] Although the neuropsychiatric comorbidities of CAE were not investigated in the present study, the identified alterations of the frontotemporal volume and medial occipital cortical thickness in the CAE patients suggest the presence of structural brain network alterations in CAE that are associated with the neuropsychiatric comorbidities of CAE.

Unlike in previous studies,[5,8-10,44] no changes in subcortical structural volumes were found in the present patients with CAE. However, the thalamic volume changes in patients with CAE have varied among studies,[8-10] and amygdala volume reduction was related to ADHD and the frequency of absence seizures.[6] Determining the relationships between subcortical volumes, severity of absence seizures, and psychiatric comorbidities in CAE will require further well-controlled studies involving larger cohorts.

Several limitations including the smallness of the sample should be considered when interpreting the present results. Although we attempted to recruit a homogeneous group of patients who were not taking medications, the smallness of the sample that included patients of various ages and handedness reduced the reliability of our results. Another limitation is that cross-sectional imaging analyses cannot reveal the associations of structural alterations with seizures and cognitive variables. This study did not analyze the frequency of seizures, the variable time intervals between the onset of seizures and the brain MRI investigations, or comorbid psychiatric problems, which are possible confounding factors.

Further longitudinal studies with neurocognitive measurements are needed to advance the understanding of abnormal trajectories of cortical development and their relationships with seizure outcomes and cognitive and behavioral functions in patients with CAE.

This study revealed the presence of structural abnormalities with volume reduction in the bilateral frontotemporal regions and increased thickness of the posterior medial cortices in patients with CAE. These findings also suggest that altered structural networks including the frontal and parietal cortices are related to frequent and short losses of consciousness with generalized spike-and-wave discharges in CAE. Larger longitudinal studies are required to better clarify the links between structural abnormalities and clinical, neuropsychological, and electrophysiological data in absence epilepsy syndromes.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.4.573.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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